Access DB# 83360

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Samuel Wei Liu Examiner #: 79120 Date: 12-31-2002
Art Unit: 1653 Phone Number 30 6-3483 Serial Number: 09/975923
Mail Box and Bldg/Room Location: 9B01/9D08 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. 1 of 1

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

***For Sequence Searches Only** Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search cyclic peptide structure of Formula I (claim 1)
(for the limitations, please see the attached copy).
X= absent

Thanks!
Samuel

Point of Contact:
Susan Hanley
Technical Info. Specialist
CM1 6B05 Tel: 305-4053

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Hanley	NA Sequence (#)		STN	
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)	1	Questel/Orbit	
Date Searcher Picked Up: 1/2	Bibliographic		Dr.Link	
Date Completed: 1/8	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time:	Other		Other (specify)	

PTO-1590 (8-01)

Claims

What is claimed is:

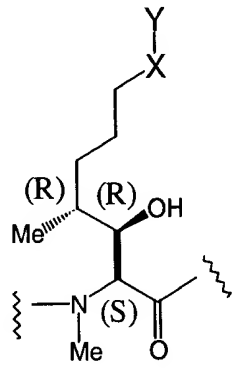
1. A cyclosporin analog of formula (I) or a pro-drug or a pharmaceutically acceptable salt thereof:

A---B---Sar-MeLeu-Val-MeLeu-Ala---U---MeLeu-MeLeu-MeVal
1 2 8

(I)

wherein,

(a) A is of the formula:



wherein

(1) X is absent, -C1-C6 alkyl-, or –C3-C6 cycloalkyl-;

Y is selected from the group consisting of:

i. -C(O)-O-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio;

(2) Y = $COOCH_3$

ii. -C(O)-S-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio;

iii. -C(O)-OCH_2-OC(O)R2 where R2 is C1-C6 alkyl, optionally substituted with halogen, C1-C6 alkoxy, C1-C6 alkylthio, heterocyclics or aryl;

iv. -C(S)-O-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio; and

v. C(S)-S-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio.

(b) B is –αAbu-, -Val-, -Thr- or –Nva-; and

(c) U is –(D)Ala-, -(D)Ser- or –[O-(2-hydroxyethyl)(D)Ser]-; or -[O-acyl(D)Ser]- or –[O-(2-acyloxyethyl)(D)Ser]-.

2. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula (I), B is -αAbu-, and U is -(D)Ala-.

3. A cyclosporin analog according to Claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, wherein in formula I:

(i) A is of the formula A1 or A2, wherein:

X is absent; and

Y is selected from a group consisting of:

i. -C(O)-O-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio;

ii. -C(O)-S-R1 where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio, halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio; and

iii. C(O)-OCH_2-OC(O)R2 where R2 is C1-C6 alkyl optionally substituted with halogen, C1-C6 alkoxy, C1-C6 alkylthio, heterocyclics or aryl;

(ii) B is -αAbu-; and

(iii) U is -(D)Ala-.

4. A cyclosporin analog according to claim 1 or a pro-drug or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -COOH;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -COOEt;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2CH_2CH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2Ph$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2F$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCHF_2$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCF_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2CF_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2Cl$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2OCH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$COOCH_2OCH_2CH_2O\ CH_3$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -$C(=O)SCH_2Ph$;

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is -$CH_2CH_2CH_2$-, Y = -$COOCH_3$; and

Compound of Formula (I) wherein B = –αAbu-, U = –(D)Ala-, X is absent, Y = -COOFmoc.

5. A chemical process for preparing a cyclosporin analog of formula I as claimed in Claim 1, comprising:
   a. reacting a compound of formula I, wherein A= -MeBmt- with:
      i. an olefin of formula CH_2=CH-X-Y, wherein X and Y are as defined in Claim 1; and
      ii. a catalyst;
      in the presence of a lithium salt in an organic solvent; and
   b. hydrogenating the product of step a in an organic solvent under hydrogen with a catalyst;
      and optionally converting the product of said reaction into a pharmaceutically acceptable salt.

6. The chemical process as claimed in Claim 5, wherein the catalyst in step (a) (ii) is Grubb's ruthenium alkylidene, Nolan's catalyst, a benzylidene catalyst or a molybdenum catalyst.

7. The chemical process as claimed in Claim 5, wherein step (b) is performed at room temperature.

8. The chemical process as claimed in Claim 7, wherein the catalyst in step (b) is Palladium on carbon.

9. A pharmaceutical composition, said composition comprising at least one cyclosporin analog of formula 1 as claimed in Claim 1, said cyclosporin analog being present alone or in combination with a pharmaceutically acceptable carrier or excipient.

10. A method for treating diseases characterized by airflow obstruction in a subject in need of treatment which comprises the step of administering to said subject a therapeutically effective amount of at least one cyclosporin analog of formula I as claimed in Claim 1.

11. The method of Claim 10, wherein said disease is asthma.

12. The method of Claim 10, wherein the step of administering the cyclosporin analog of formula I is done by topical administration.

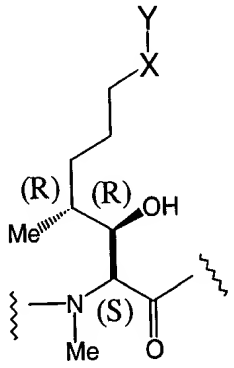
Abstract

the present invention relates to a cyclosporin analog of the following formula (I) or a pro-drug or pharmaceutically acceptable salt thereof:

A---B---Sar-MeLeu-Val-MeLeu-Ala---U---MeLeu-MeLeu-MeVal
1 2 3 8 11

(I)

In formula I, the formula for residue A is:



where X is absent, -C1-C6 alkyl-, or –C3-C6 cycloalkyl-; Y is selected from the groups: -C(O)-O-R1; -C(O)-S-R1; -C(O)-OCH_2-OC(O)R2; -C(S)-O-R1; and -C(S)-S-R1; where R1 is hydrogen, C1-C6 alkyl optionally substituted with halogen, heterocyclics, aryl, C1-C6 alkoxy or C1-C6 alkylthio or halogen substituted C1-C6 alkoxy, halogen substituted C1-C6 alkylthio and where R2 is C1-C6 alkyl optionally substituted with halogen, C1-C6 alkoxy, C1-C6 alkylthio heterocyclics or aryl; B is -αAbu-, -Val-, -Thr- or -Nva-; and U is –(D)Ala-, -(D)Ser- or –[O-(2-hydroxyethyl)(D)Ser]-, or -[O-acyl(D)Ser]- or –[O-(2-acyloxyethyl)(D)Ser]-.

In a second embodiment, the present invention relates to the use of the cyclosporin analogs of the present invention or a pro-drug or pharmaceutically acceptable salt thereof in pharmaceutical compositions for the treatment of asthma and other diseases characterized by airflow obstruction in a subject. In a third embodiment, the present invention relates to processes for the production of novel cyclosporin analogs of the present invention. The present invention also contemplates method(s) of treatment of asthma and other diseases characterized by airflow obstruction in a subject by administering to the subject therapeutically effective amounts of the cyclosporin analogs of the present invention with or without the concurrent use of other drugs or pharmaceutically acceptable carriers or excipients.

① Registry Search

LIU 09/975,923

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L5               STR
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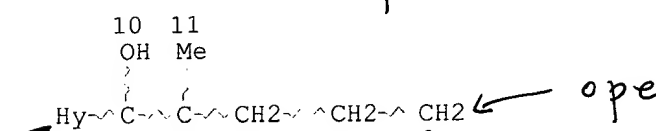
parent STRUCTURE



← open, anything can attach here

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DEFAULT ECLEVEL IS LIMITED
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NUMBER OF NODES IS   8

STEREO ATTRIBUTES: NONE
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L7               STR
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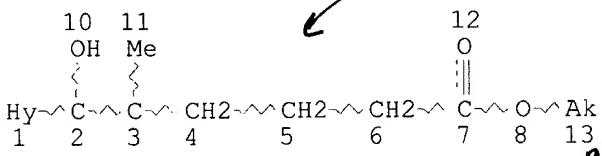
Hy must be a heteroring w/ 22 C's & 11 N's - this forces it to be a cyclosporin ring

54 cpds fit L5

Sub set STR searched against L6 answer set



← isolated alkyl group

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* NO COMPOUNDS * for this specie

(2) parent search for reg file

LIU 09/975,923

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L2             STR

    10  11
    OH  Me

Hy-  C-  C-  CH2-  CH2-  CH2
1    2   3   4     5     6

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DEFAULT ECLEVEL IS LIMITED
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NUMBER OF NODES IS   8

STEREO ATTRIBUTES: NONE
L3           54 SEA FILE=REGISTRY SUB=L1 SSS FUL L2
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since there are no hits for the specific, I am giving you the "d scan" print out of the 54 cpds from the parent search in the Regfile

If you want to pursue any of these - give me a call.

```
=> d scan l3

L3   54 ANSWERS   REGISTRY  COPYRIGHT 2003 ACS
IN   Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic
     acid]-7-[O-(3-carboxy-1-oxopropyl)-L-threonine]- (9CI)
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MF   C66 H117 N11 O16

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
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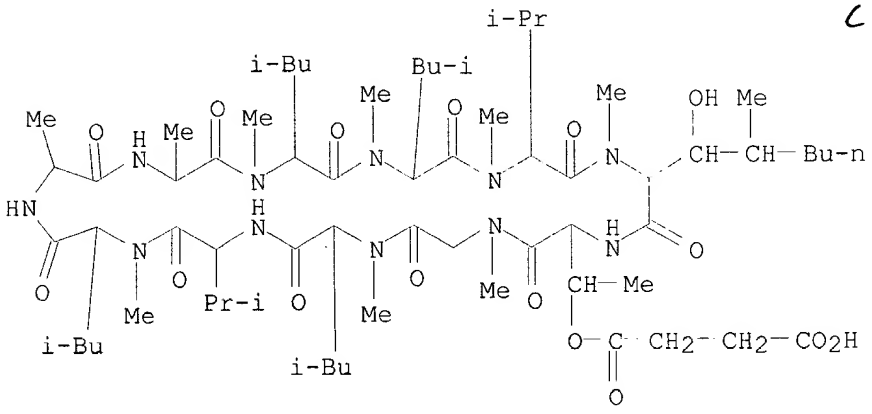
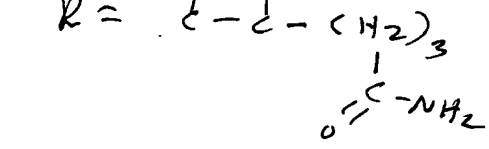
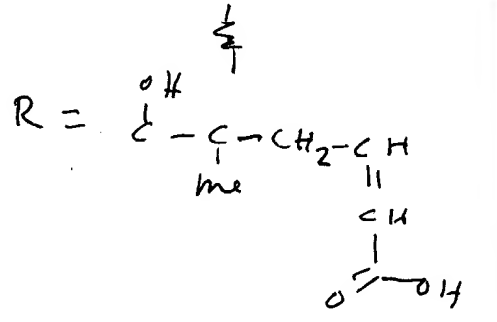


I retrieved the citations for 2 cpds that I thought were close





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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):53

L3   54 ANSWERS   REGISTRY  COPYRIGHT 2003 ACS
IN   Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminononanoic
     acid]-7-L-norvaline- (9CI)
SQL  11
MF   C64 H117 N11 O12
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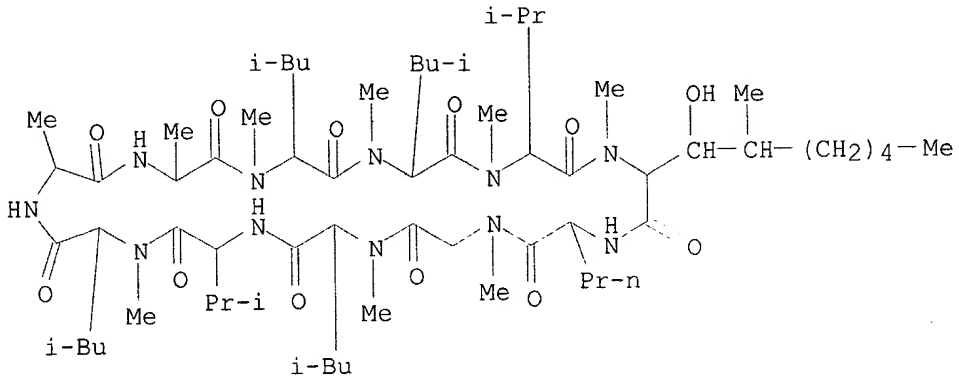

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-(O-acetyl-D-serine)-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-threonine- (9CI)
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MF C64 H115 N11 O15

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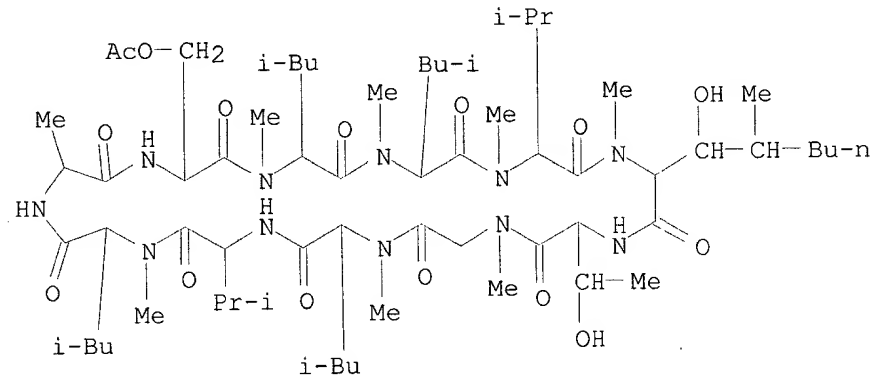

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-D-serine-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-norvaline- (9CI)
SQL 11
MF C63 H115 N11 O13

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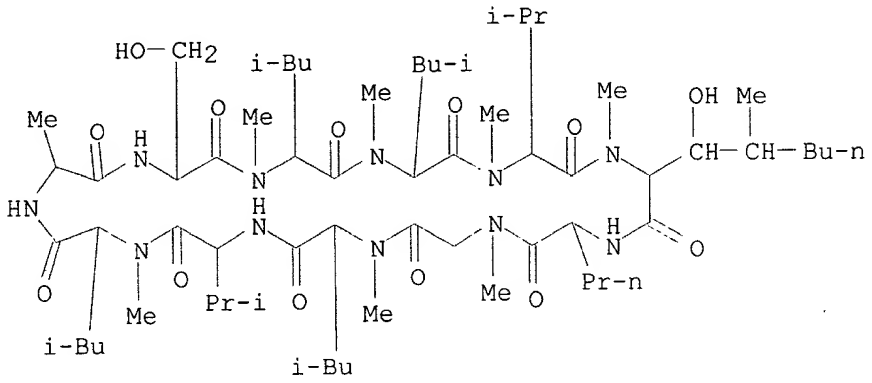

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SQL 11
MF C63 H115 N11 O12

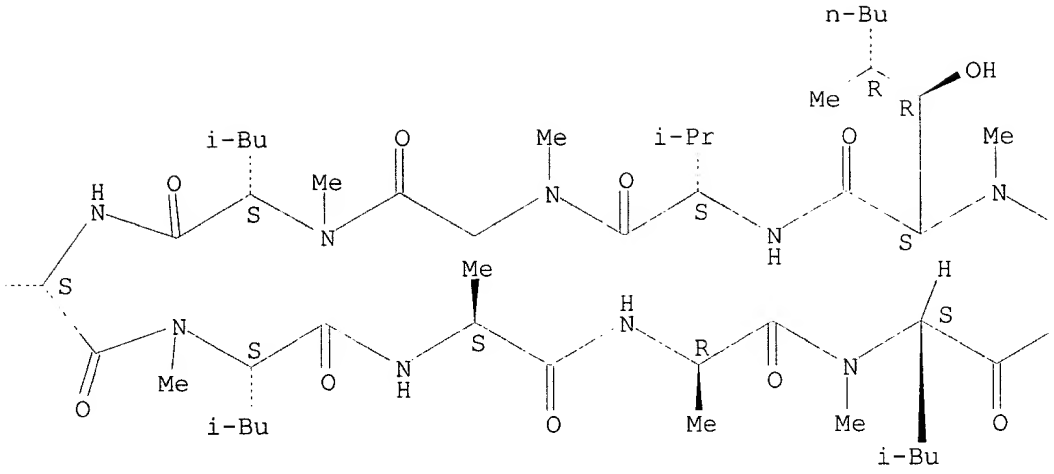
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A

i-Pr

PAGE 1-B



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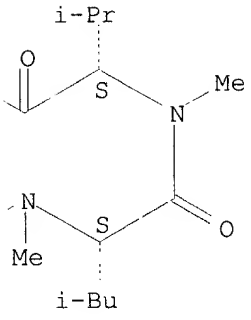

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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SQL 11
MF C87 H130 N12 O20

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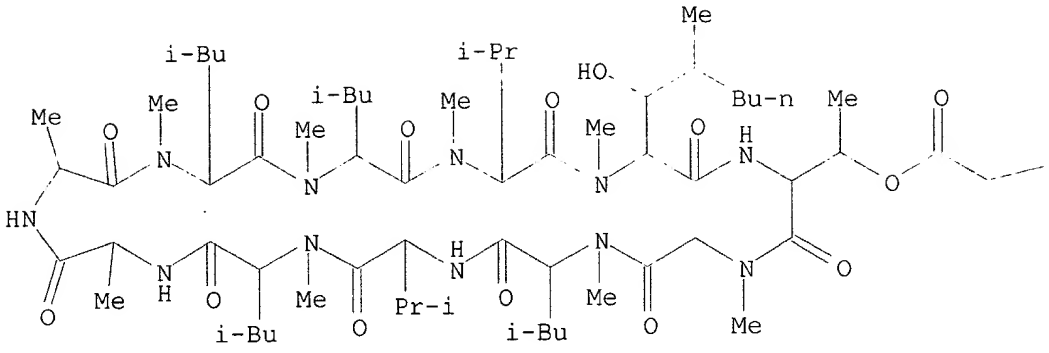
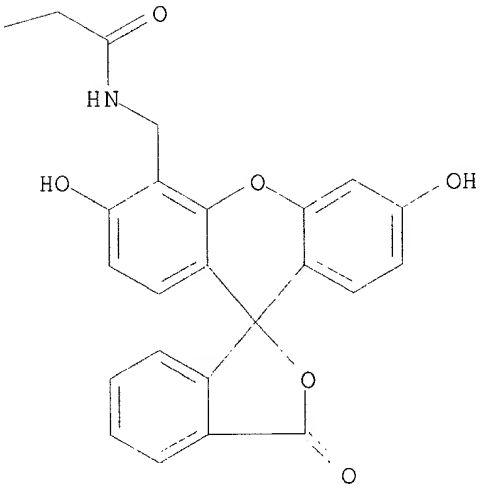
PAGE 1-A



PAGE 1-B



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminononanoic acid]-7-L-valine- (9CI)
SQL 11
MF C64 H117 N11 O12

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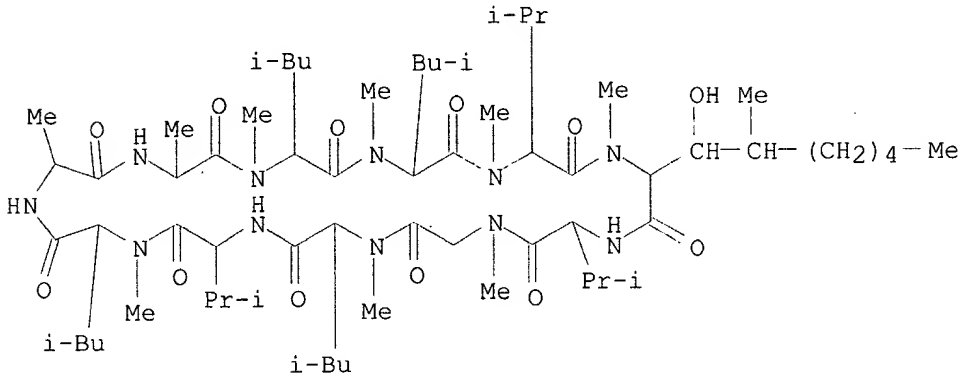

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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MF C69 H118 N12 O14

RELATED SEQUENCES AVAILABLE WITH SEQLINK

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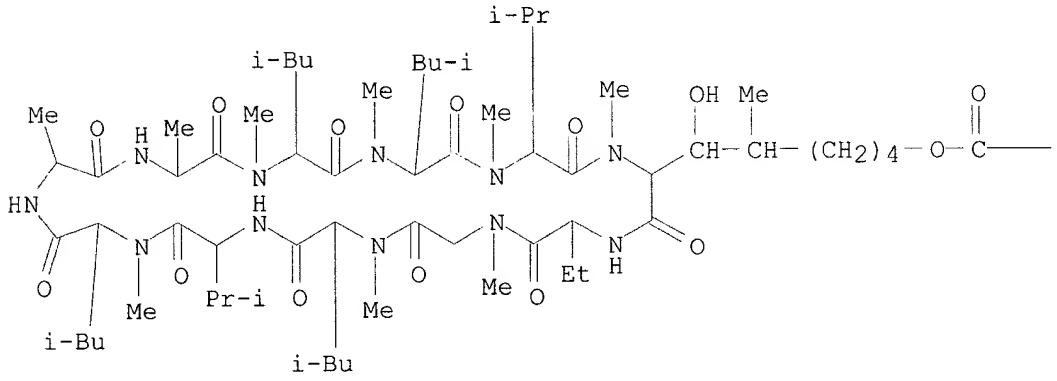

PAGE 1-B

— NHPh

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-D-threonine-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C63 H115 N11 O13

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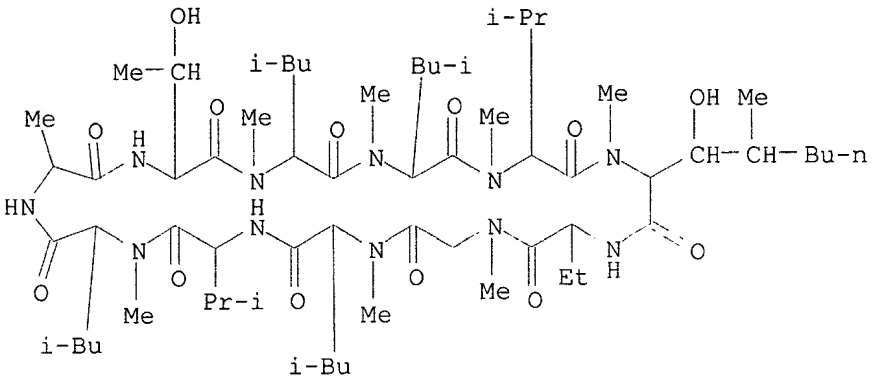

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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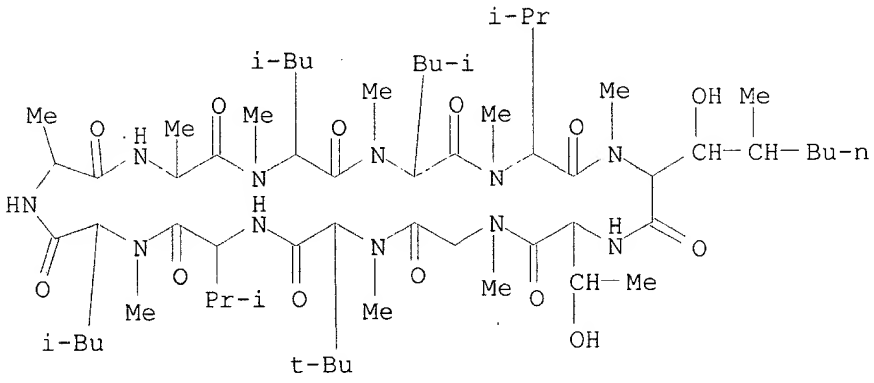

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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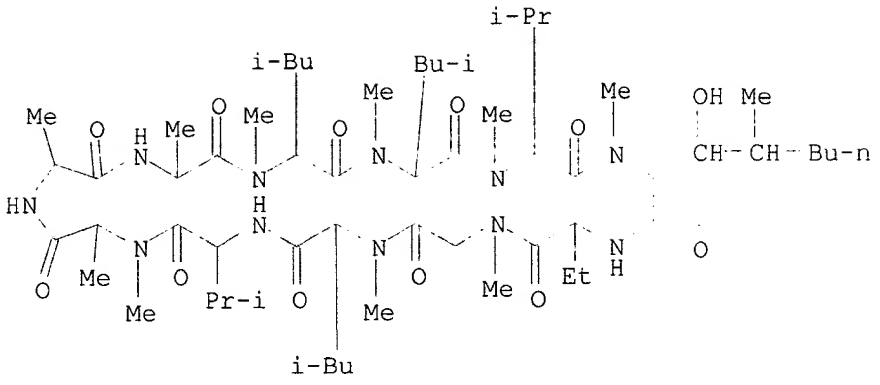

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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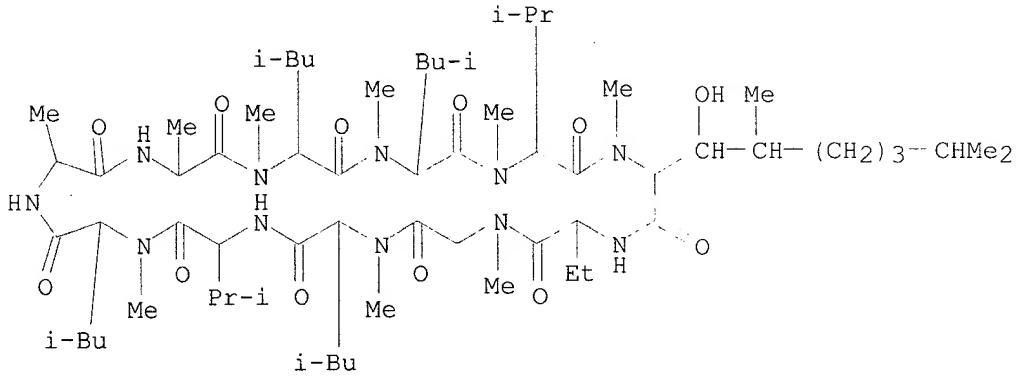

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
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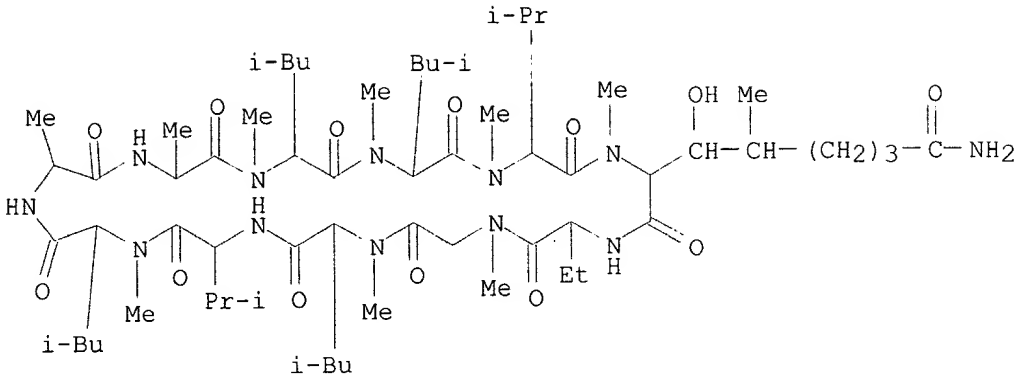

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-(O-acetyl-D-serine)-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine- (9CI)
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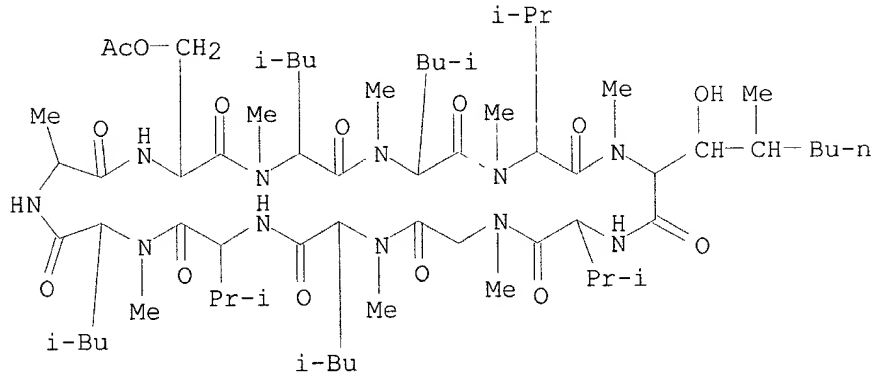


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]- (9CI)
SQL 11
MF C62 H113 N11 O12
CI COM

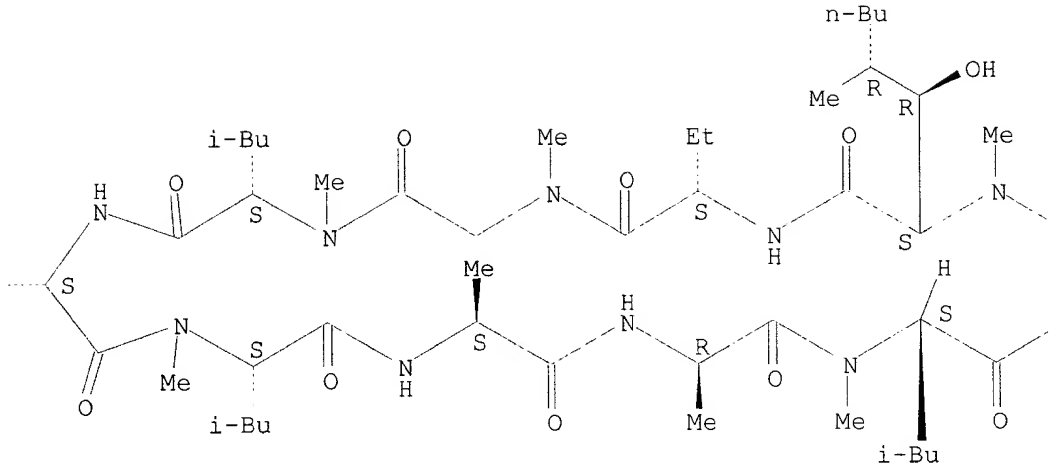
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A

i-Pr

PAGE 1-B



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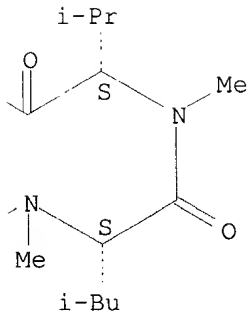
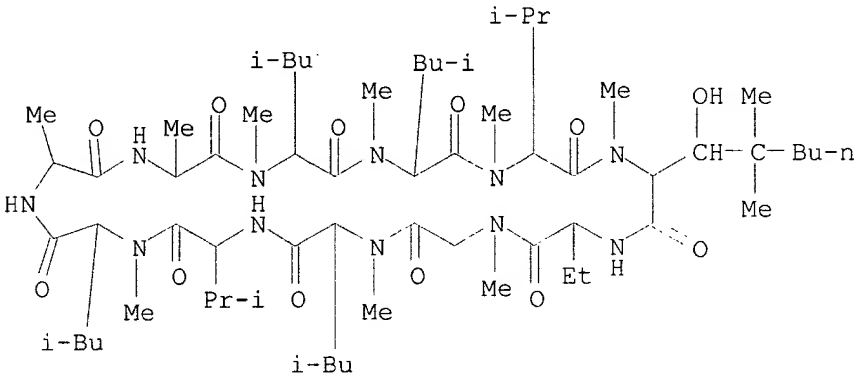


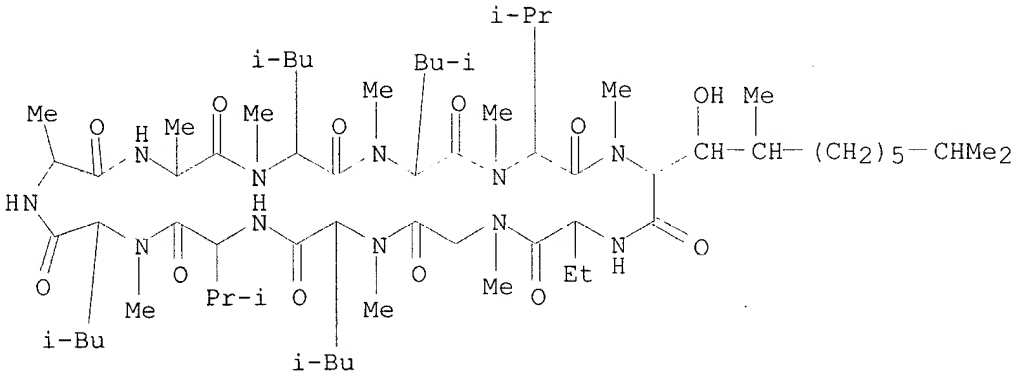
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(R)-3-hydroxy-N,4,4-trimethyl-L-2-aminooctanoic acid]- (9CI)
MF C63 H115 N11 O12



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

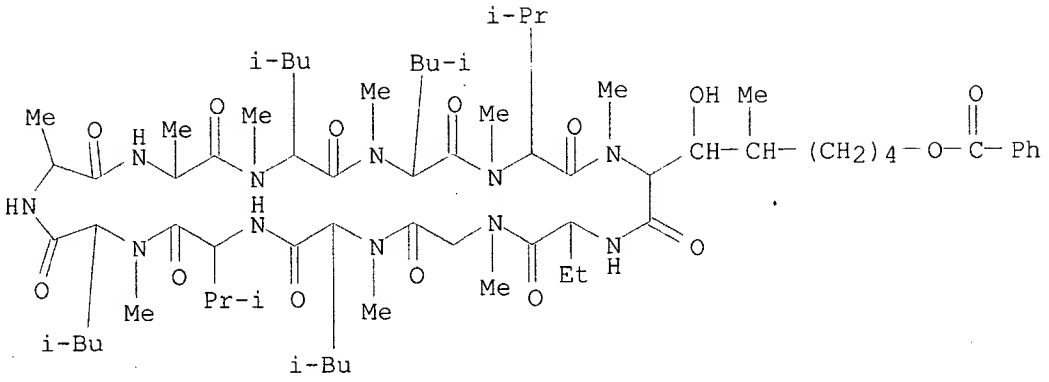
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4,10-trimethyl-L-2-aminoundecanoic acid]- (9CI)
SQL 11
MF C66 H121 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



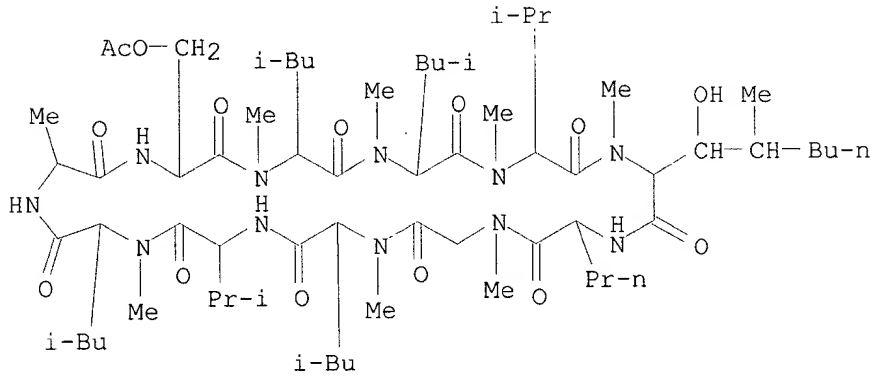
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-8-(benzoyloxy)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C69 H117 N11 O14

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-(O-acetyl-D-serine)-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-norvaline- (9CI)
SQL 11
MF C65 H117 N11 O14

RELATED SEQUENCES AVAILABLE WITH SEQLINK

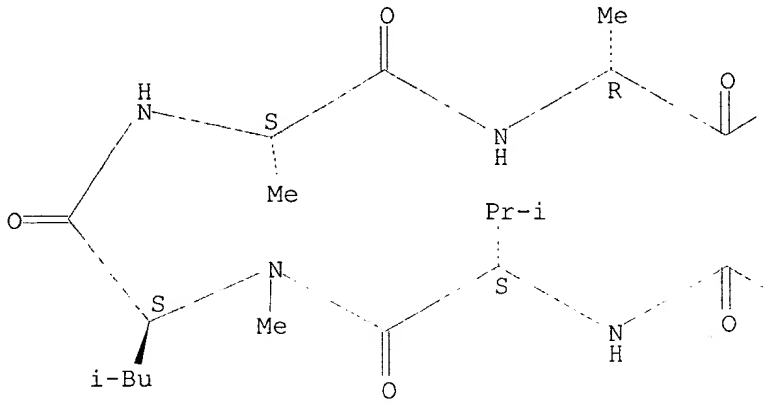


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-10-oxo-10-(propylamino)decanoic acid]- (9CI)
SQL 11
MF C67 H122 N12 O13

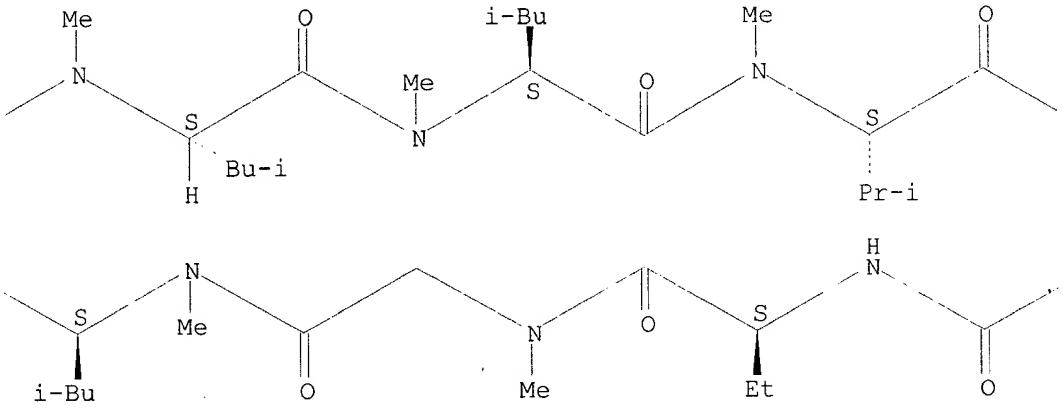
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

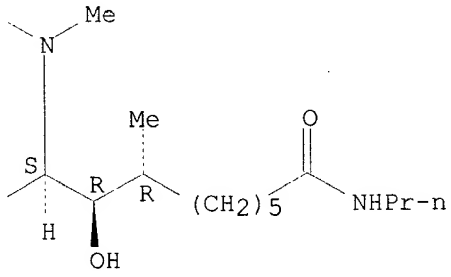
PAGE 1-A



PAGE 1-B

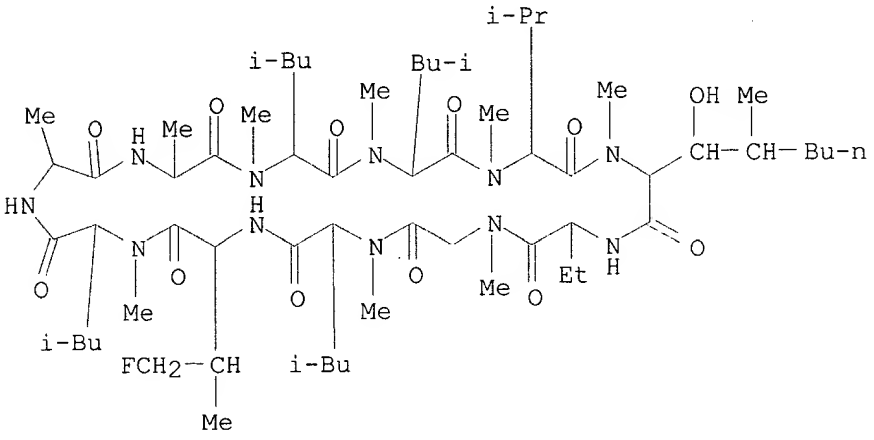


PAGE 1-C



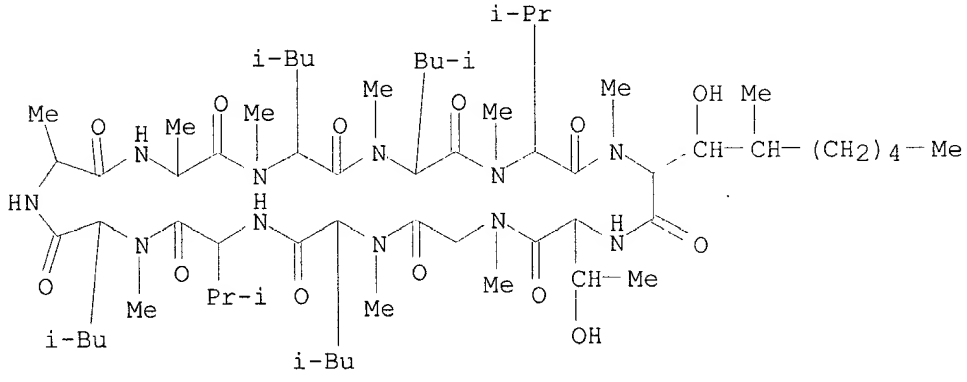
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-10-(4-fluoro-L-valine)- (9CI)
SQL 11
MF C62 H112 F N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminononanoic acid]-7-L-threonine- (9CI)
SQL 11
MF C63 H115 N11 O13

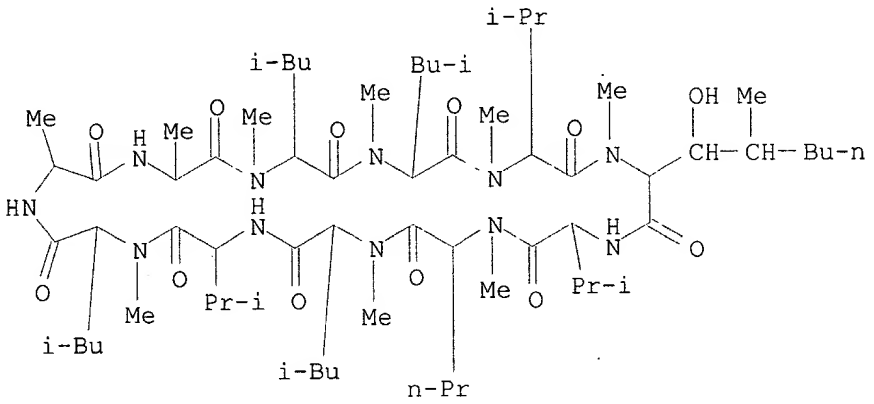
RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine-8-(N-methyl-D-norvaline)- (9CI)
SQL 11

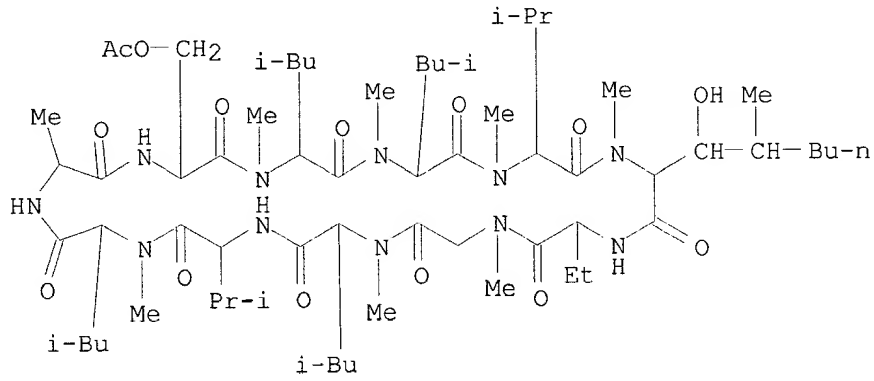
MF C66 H121 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-(O-acetyl-D-serine)-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C64 H115 N11 O14

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]-, compd. with 2-methoxy-2-methylpropane (1:2) (9CI)
SQL 11
MF C62 H113 N11 O12 . 2 C5 H12 O

RELATED SEQUENCES AVAILABLE WITH SEQLINK

CM 1

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

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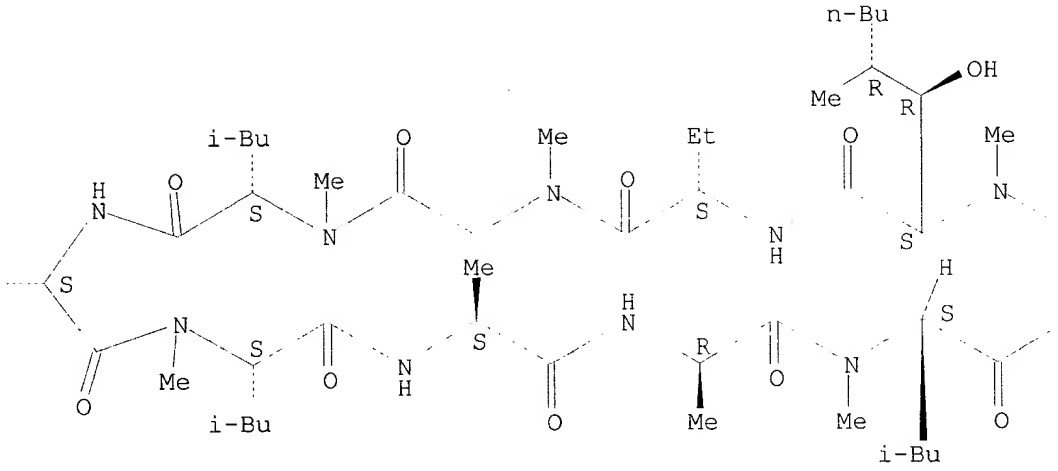
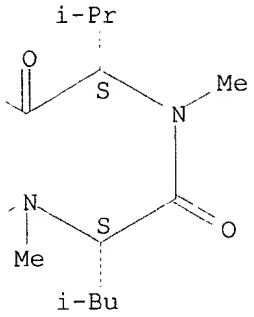


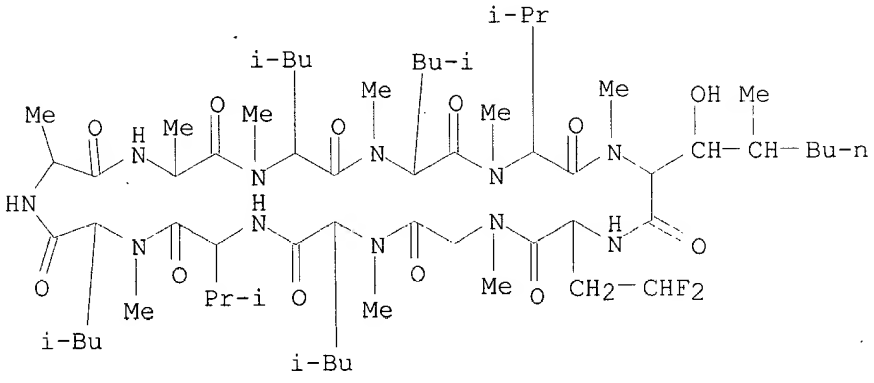


CM 2

t-Bu—O—Me

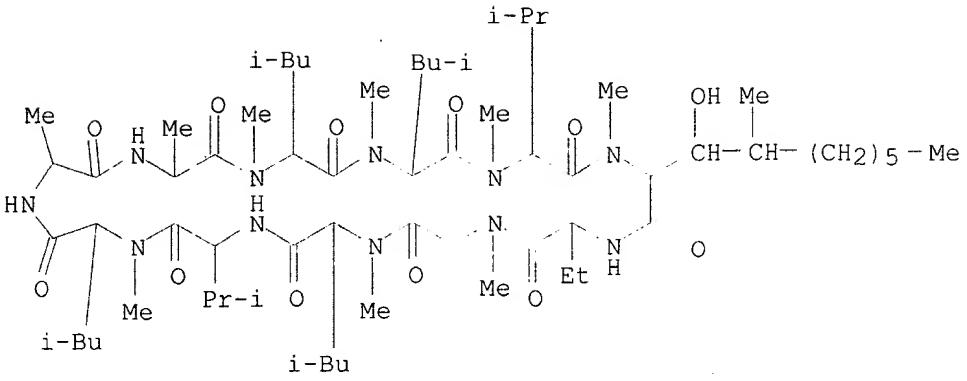
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-(4,4-difluoro-L-2-aminobutanoic acid)- (9CI)
SQL 11
MF C62 H111 F2 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



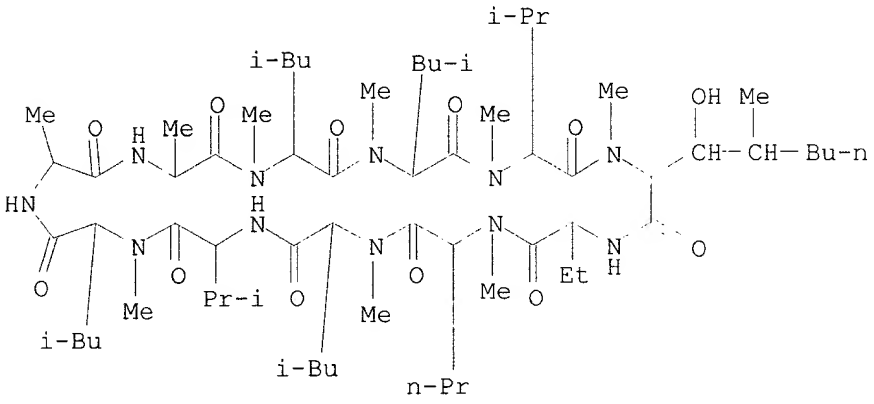
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminodecanoic acid]-(9CI)
SQL 11
MF C64 H117 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



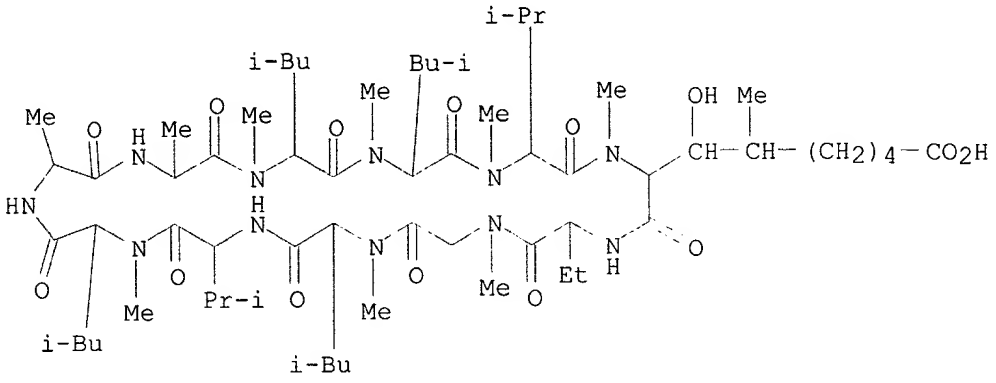
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-8-(N-methyl-D-norvaline)- (9CI)
SQL 11
MF C65 H119 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminononanedioic acid]- (9CI)
SQL 11
MF C63 H113 N11 O14

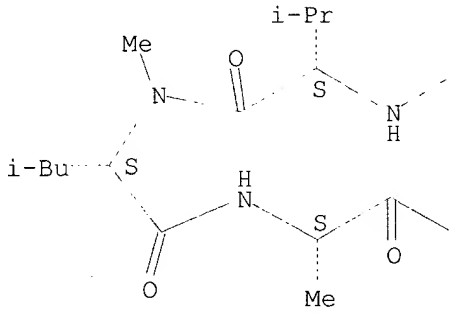
RELATED SEQUENCES AVAILABLE WITH SEQLINK



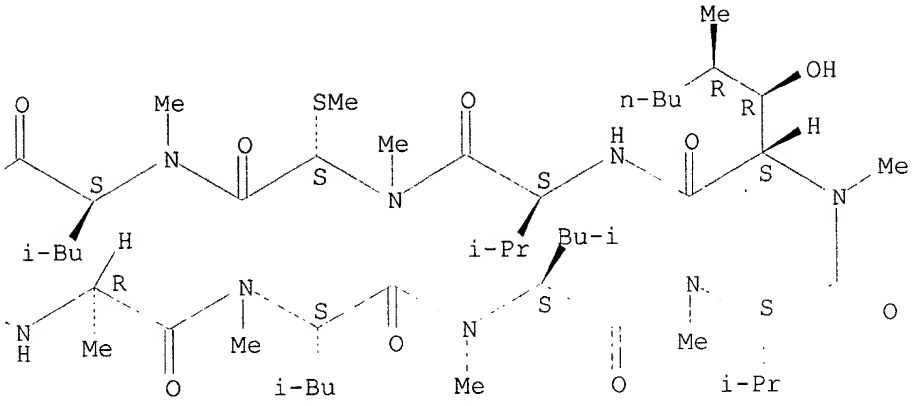
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine-8-[N-methyl-L-2-(methylthio)glycine]- (9CI)
SQL 9
MF C64 H117 N11 O12 S

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(2S,3R,4R)-3,8-dihydroxy-4-methyl-2-(methylamino)octanoic acid]- (9CI)
SQL 11
MF C62 H113 N11 O13

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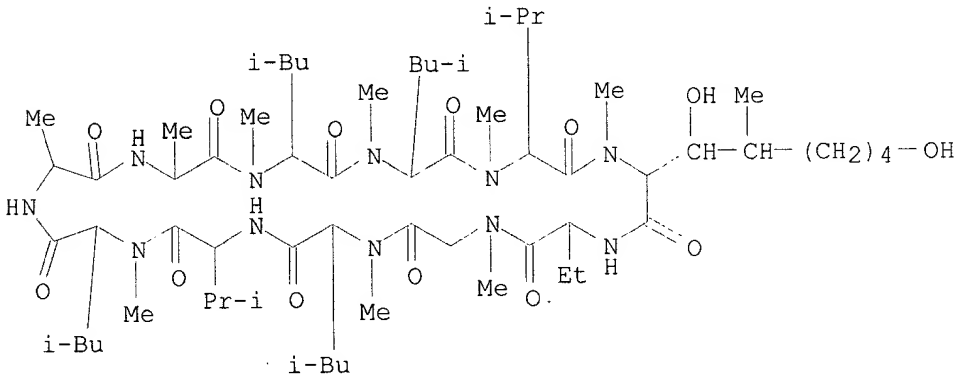
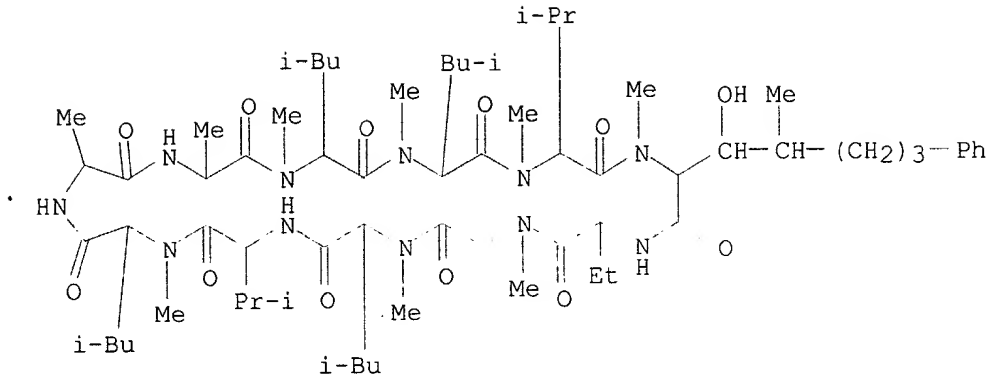


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]- (9CI)
SQL 11
MF C67 H115 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK

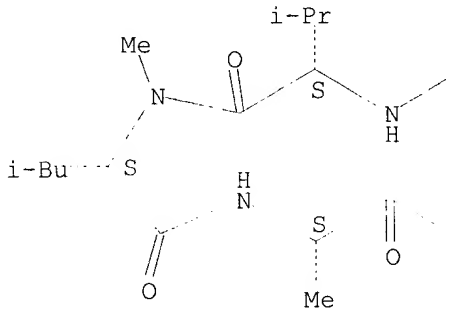


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin D, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]-8-[(2R)-N-methyl-2-(methylthio)glycine]- (9CI)
SQL 11
MF C64 H117 N11 O12 S

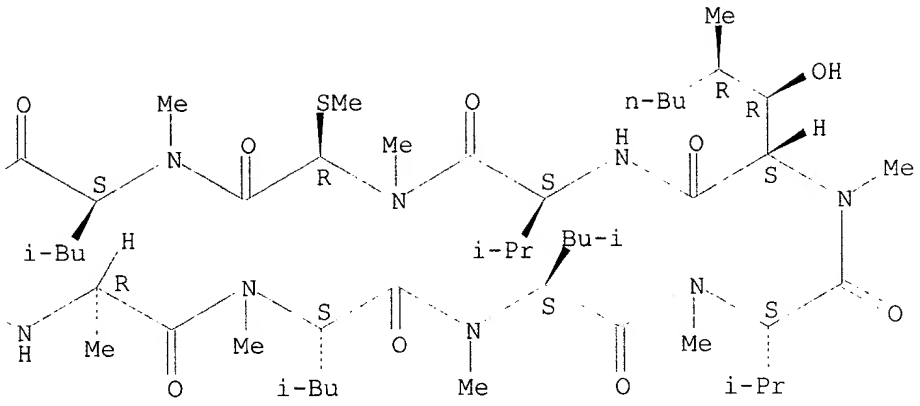
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A

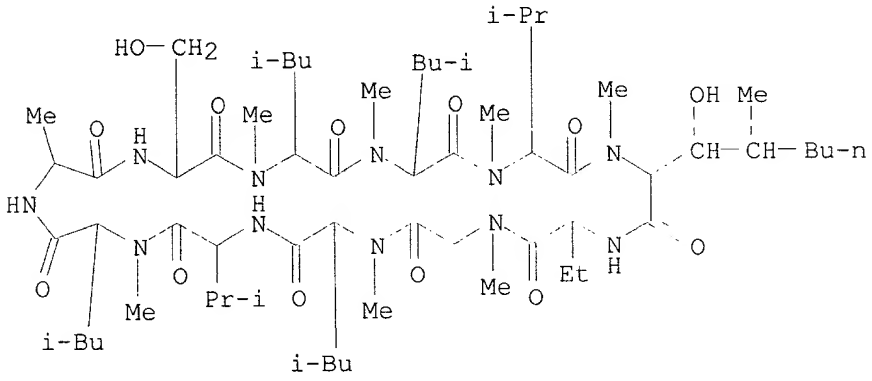


PAGE 1-B



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-D-serine-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C62 H113 N11 O13

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-8-(acetyloxy)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C64 H115 N11 O14

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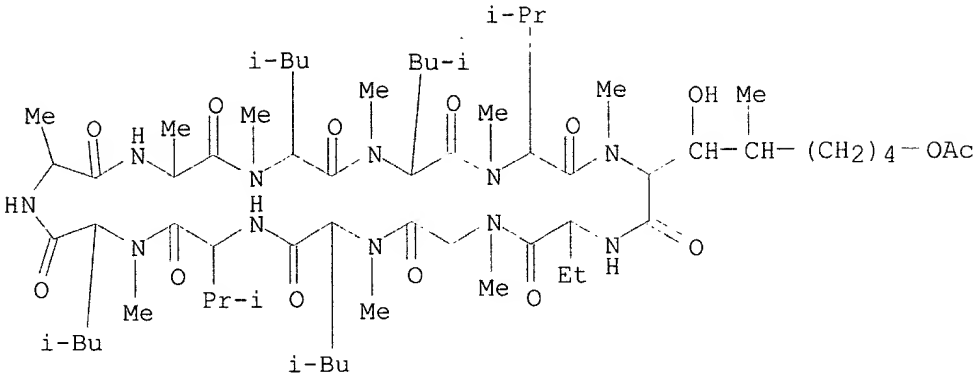

L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 3-(4-hydroxy-N-methyl-L-leucine)-6-[(3R,4R)-3,8-dihydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C62 H113 N11 O14

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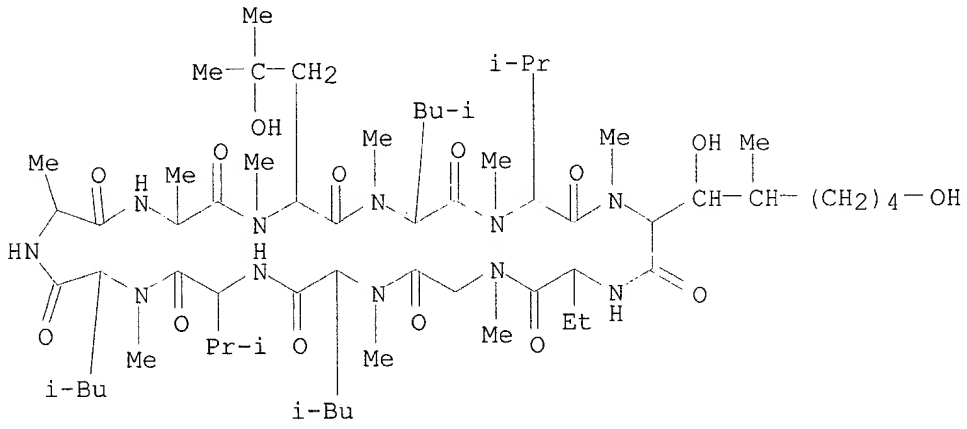
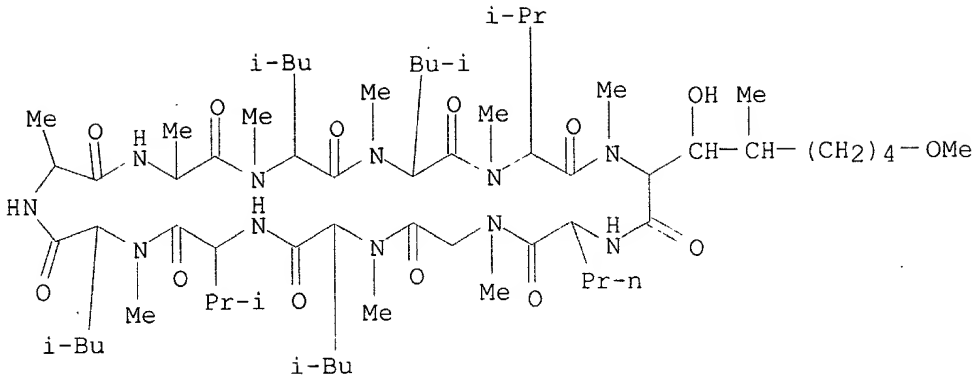


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-8-methoxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-norvaline- (9CI)
SQL 11
MF C64 H117 N11 O13

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine-8-(4,5-didehydro-N-methyl-D-norvaline)- (9CI)
SQL 11
MF C66 H119 N11 O12

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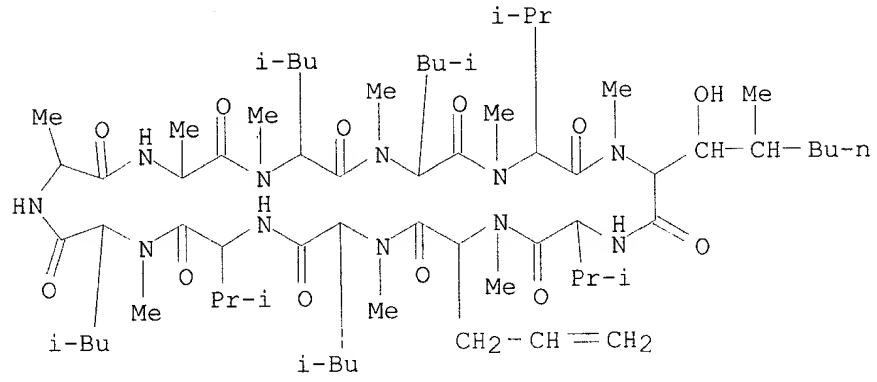
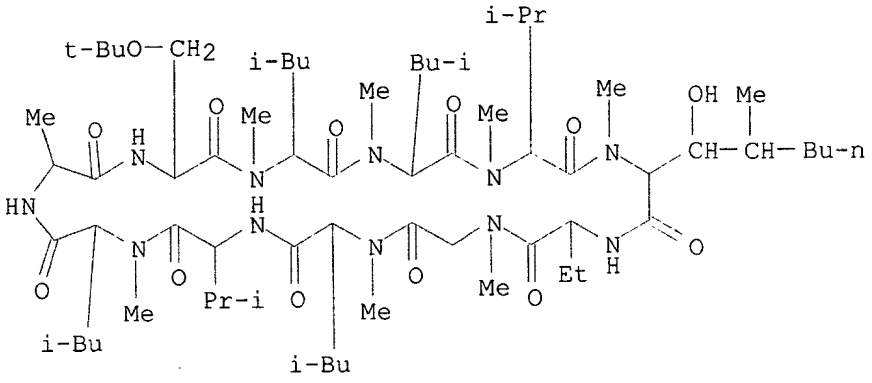


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-[O-(1,1-dimethylethyl)-D-serine]-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C66 H121 N11 O13

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-8-azido-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C62 H112 N14 O12

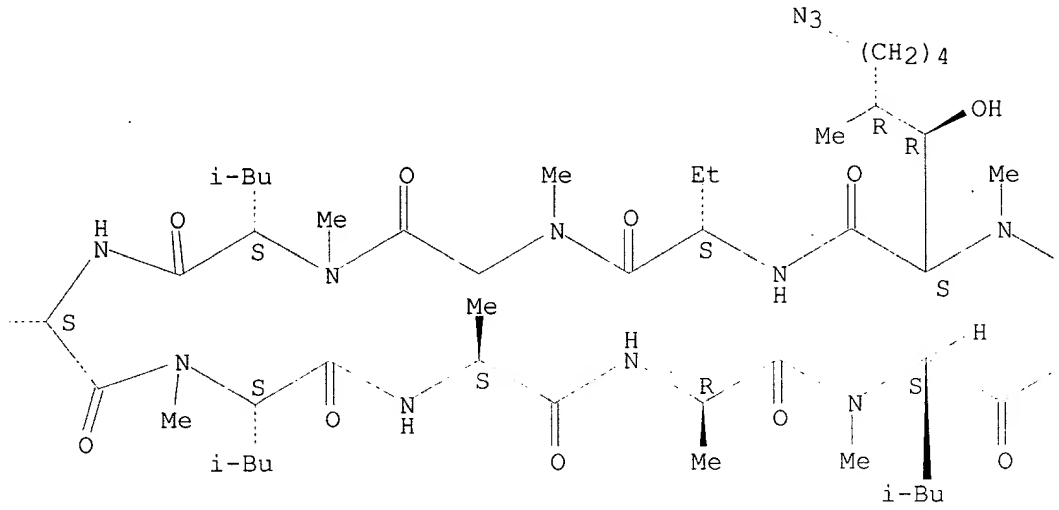
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A

i-Pr

PAGE 1-B



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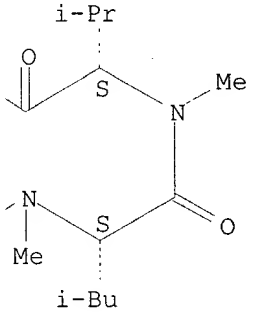
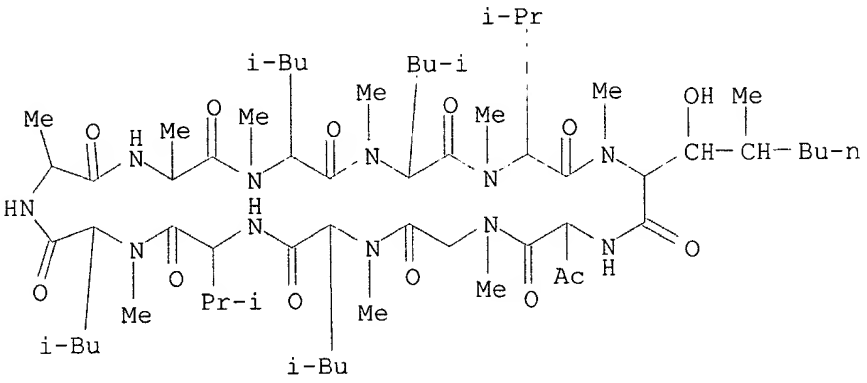


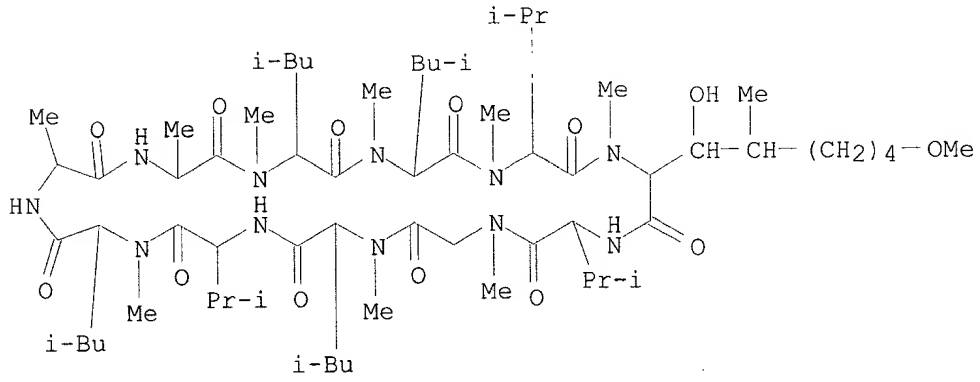
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-(3-oxo-L-2-aminobutanoic acid)- (9CI)
SQL 11
MF C62 H111 N11 O13

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-8-methoxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine- (9CI)
SQL 11
MF C64 H117 N11 O13

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-8-(4,5-didehydro-N-methyl-D-norvaline)- (9CI)
SQL 11
MF C65 H117 N11 O12

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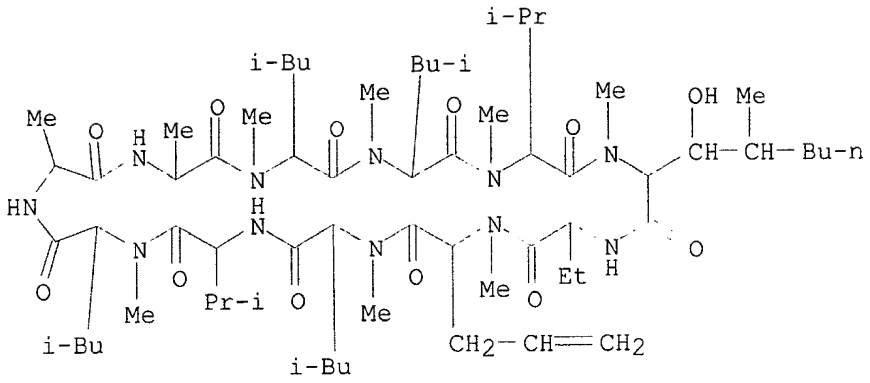


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 5-(N-methyl-D-valine)-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI)
SQL 11
MF C62 H113 N11 O12

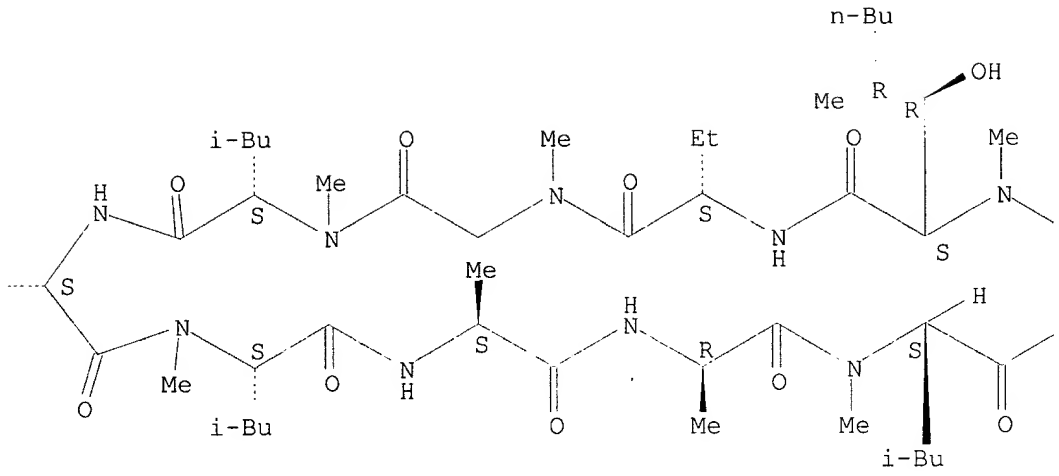
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

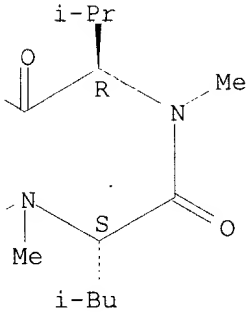
PAGE 1-A

i-Pr

PAGE 1-B

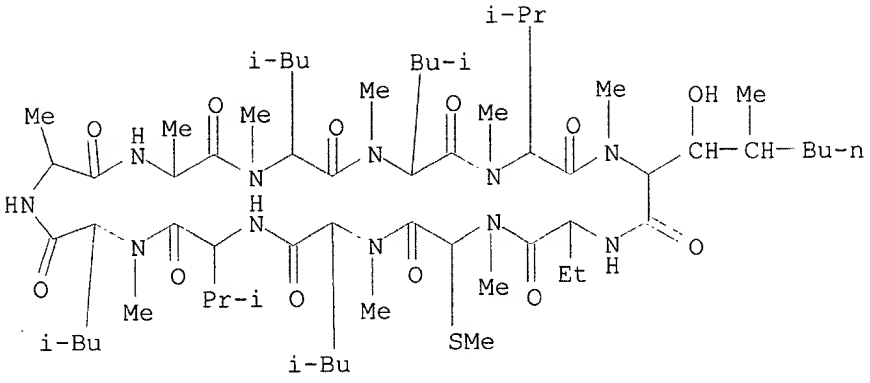


PAGE 1-C



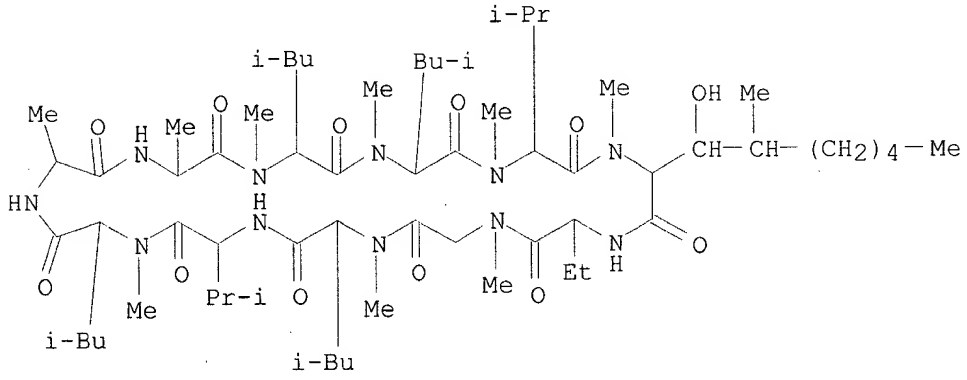
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-8-[N-methyl-(R)-2-(methylthio)glycine]- (9CI)
SQL 11
MF C63 H115 N11 O12 S

RELATED SEQUENCES AVAILABLE WITH SEQLINK



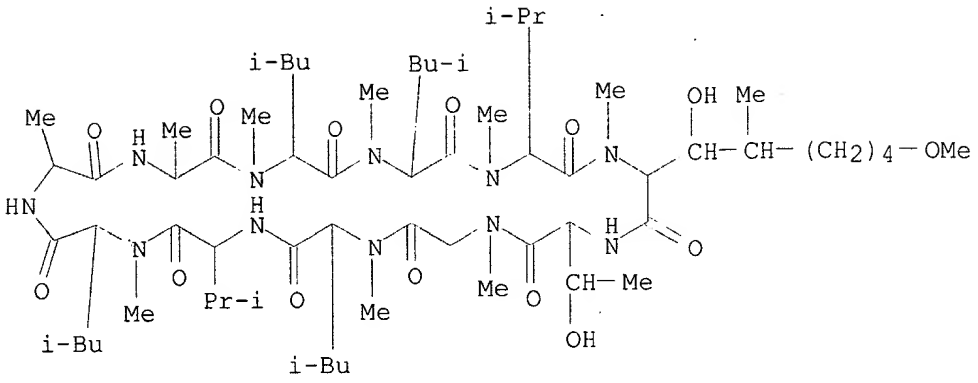
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminononanoic acid]-(9CI)
SQL 11
MF C63 H115 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



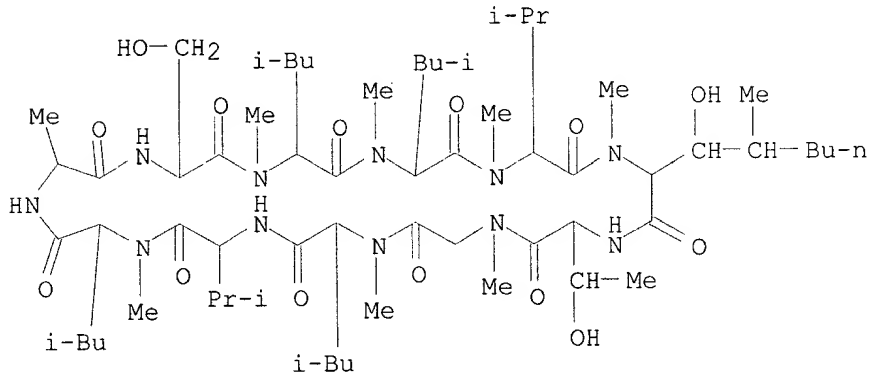
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-8-methoxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-threonine- (9CI)
SQL 11
MF C63 H115 N11 O14

RELATED SEQUENCES AVAILABLE WITH SEQLINK



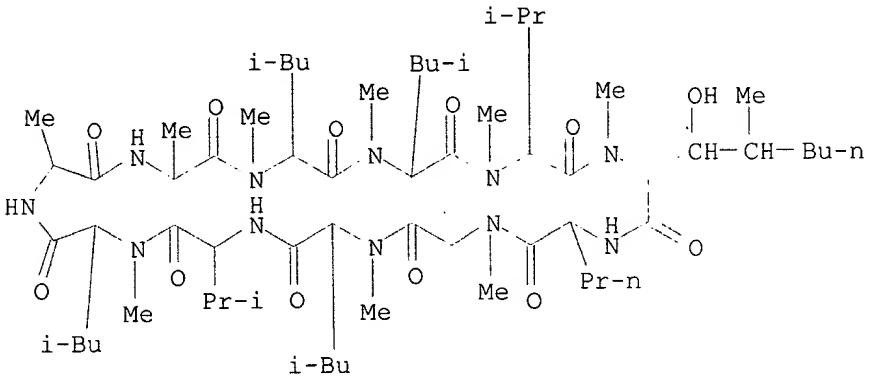
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-D-serine-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-threonine- (9CI)
SQL 11
MF C62 H113 N11 O14

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin G, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]- (9CI)
SQL 11
MF C63 H115 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK

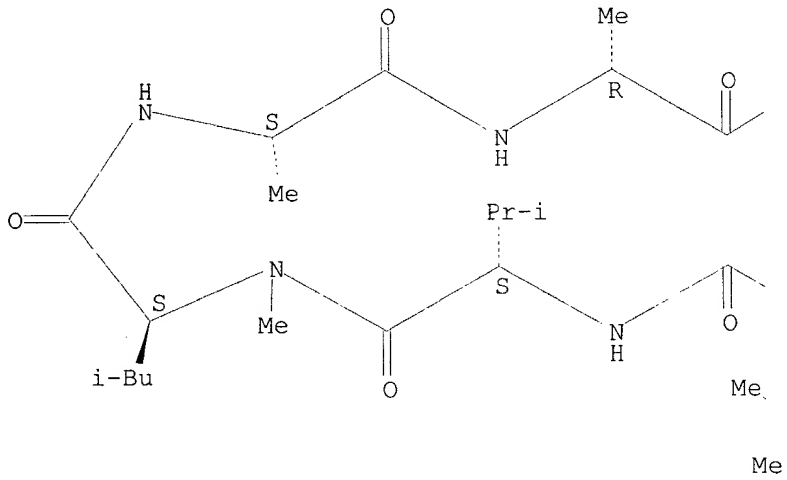


L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(2S,3R,4R)-2-amino-3-hydroxy-N,4-dimethyloctanoic acid]-9-(4-hydroxy-N-methyl-L-leucine)- (9CI)
SQL 11
MF C62 H113 N11 O13

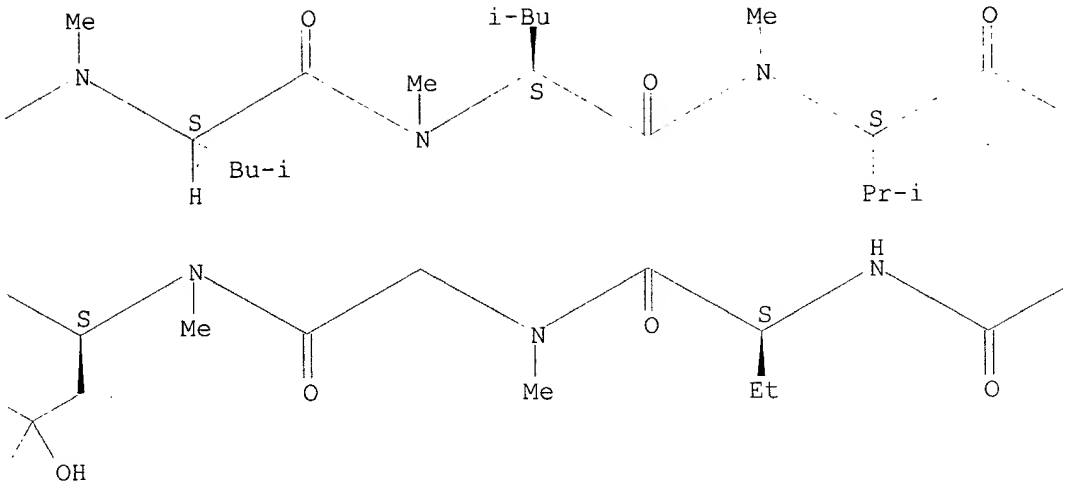
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

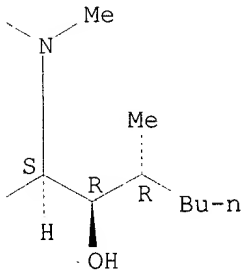
PAGE 1-A



PAGE 1-B

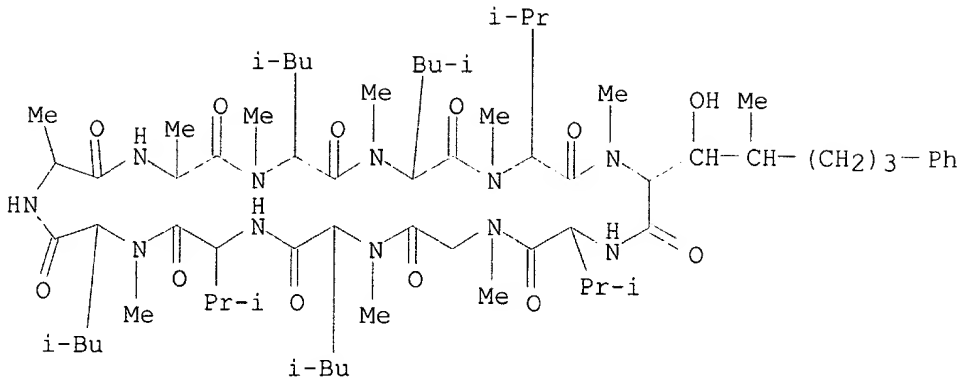


PAGE 1-C



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N,4-dimethyl-7-phenyl-L-2-aminoheptanoic acid]-7-L-valine- (9CI)
SQL 11
MF C68 H117 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 6-[(2S,3R,4R)-3-hydroxy-8-methoxy-4-methyl-2-(methylamino)octanoic acid]- (9CI)
SQL 11
MF C63 H115 N11 O13

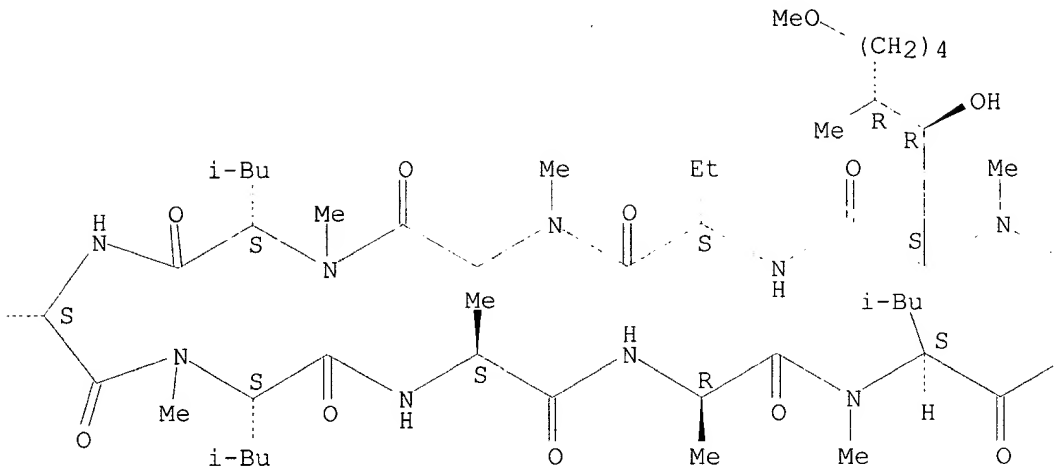
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

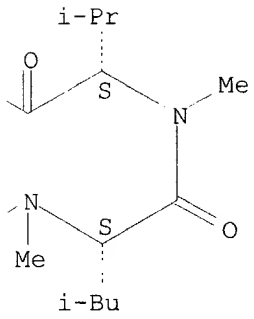
PAGE 1-A

i-Pr

PAGE 1-B

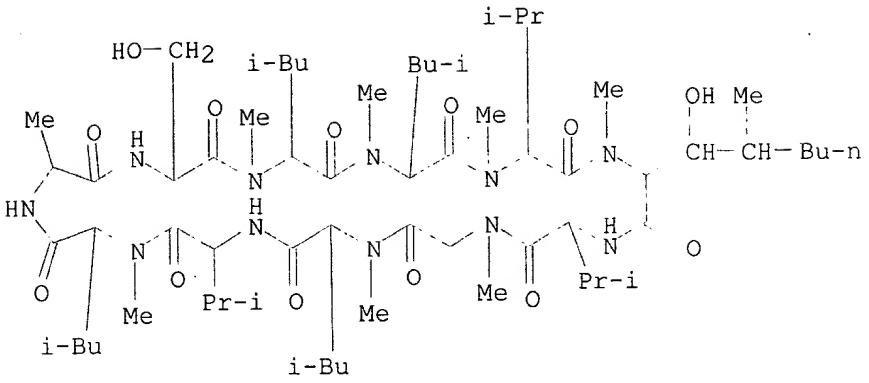


PAGE 1-C



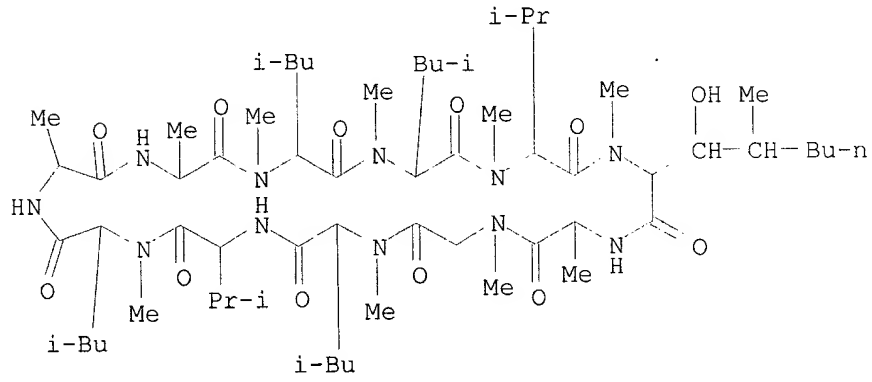
L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin A, 2-D-serine-6-[(3R,4R)-3-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-7-L-valine- (9CI)
SQL 11
MF C63 H115 N11 O13

RELATED SEQUENCES AVAILABLE WITH SEQLINK



L3 54 ANSWERS REGISTRY COPYRIGHT 2003 ACS
IN Cyclosporin B, 6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]- (9CI)
SQL 11
MF C61 H111 N11 O12

RELATED SEQUENCES AVAILABLE WITH SEQLINK



ALL ANSWERS HAVE BEEN SCANNED

(3) citations for "close" cpds

LIU 09/975,923

```
=> d que l26
L22             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  137500-57-3
L23             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  114865-26-8
L24             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22
L25             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23
L26             2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L24 OR L25)
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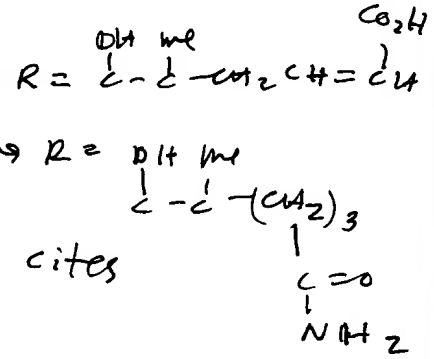


2 cites

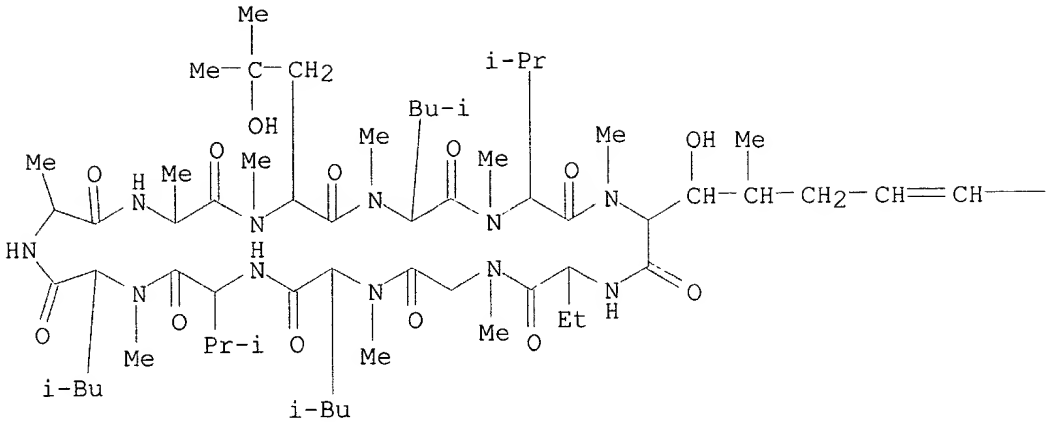
=> d ibib abs hitstr 1

L26 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:669869 HCAPLUS
DOCUMENT NUMBER: 115:269869
TITLE: Investigations on the metabolic pathways of cyclosporine: II. Elucidation of the metabolic pathways in vitro by human liver microsomes
AUTHOR(S): Christians, U.; Strohmeyer, S.; Kownatzki, R.; Schiebel, H. M.; Bleck, J.; Kohlhaw, K.; Schottmann, R.; Sewing, K. F.
CORPORATE SOURCE: Inst. Allg. Pharmakol., Med. Hochsch. Hannover, Hannover, Germany
SOURCE: Xenobiotica (1991), 21(9), 1199-210
CODEN: XENOBH; ISSN: 0049-8254
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclosporine and its metabolites, isolated from human bile and identified by FAB mass spectrometry and 1H-NMR spectroscopy, were metabolized by human liver microsomes for the identification of new cyclosporine metabolites. From these data a metabolic pathway for cyclosporine, which includes these new cyclosporine metabolites, has been proposed. The new metabolites were isolated by semipreparative HPLC and their chem. structures were elucidated by FAB mass spectrometry. These isolated metabolites were further metabolized and the products identified by FAB mass spectrometry. Fourteen metabolites, whose structure has not yet been elucidated, were isolated after metab. of structurally identified cyclosporine metabolites, and chem. structures for five of these metabolites were proposed. The structures of the new cyclosporine metabolites were: (i) a N-demethylated, carboxylated deriv. (AM1A4N), (ii) a di-hydroxylated, N-demethylated deriv. (AM14N9), (iii) a hydroxylated and carboxylated deriv. (AM1A9), (iv) a dihydroxylated, cyclized and N-demethylated deriv. (AM1c4N9) and (v) a cyclized and carboxylated (AM1cA) deriv. A proposed cyclosporine metabolic pathway comprises a total of 29 metabolites. It consists of four main branches originating from metabolites AM1, AM1c, AM9, and AM4N.

IT **137500-57-3**, Cyclosporin A metabolite 1A9
RL: BIOL (Biological study)
(as cyclosporine metabolite, in liver microsomes of humans)
RN 137500-57-3 HCAPLUS
CN Cyclosporin A, 3-(4-hydroxy-N-methyl-L-leucine)-6-[(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanedioic acid]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

—CO_2H

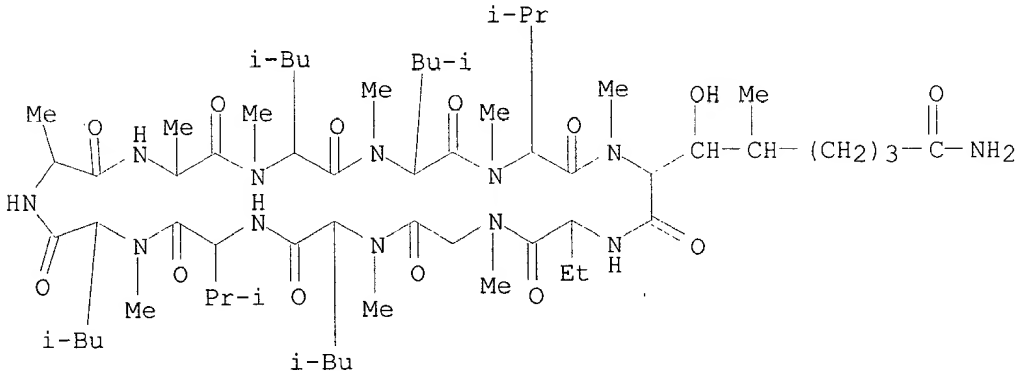
=> d ibib abs hitstr 2

L26 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1988:416575 HCAPLUS
DOCUMENT NUMBER: 109:16575
TITLE: Study of the conformation of cyclosporine in aqueous medium by means of monoclonal antibodies
AUTHOR(S): Quesniaux, Valerie F. J.; Wenger, Roland M.; Schmitter, Doris; Van Regenmortel, Marc H. V.
CORPORATE SOURCE: Lab. Immunochem., Inst. Mol. Cell. Biol., Strasbourg, 67084, Fr.
SOURCE: International Journal of Peptide & Protein Research (1988), 31(2), 173-85
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The three-dimensional structure of the immunosuppressive cyclic peptide cyclosporine (Cs), detd. in crystal by X-ray anal. and in soln. in aprotic solvents by NMR, differs mainly by the orientation of the 7 carbon side chain of residue 1. Because of its poor soly. in water, the conformation of Cs in aq. medium cannot be studied by NMR methods, which require concns. of the substance of the order of milligram/mL, but can be analyzed by immunochem. methods in which concns. in the nanogram/mL range are detected. In the present study, the ability of a series of monoclonal antibodies (McAbs) raised against Cs to recognize different parts of residue 1 of Cs was detd. from the cross-reactivity of different Cs-analogs modified in residue 1. When Cs is dissolved in aq. buffer, the terminal atoms of residue 1 side chain are not available for binding to antibodies recognizing the face of the mol. defined by residues 1, 2, 3, 10, 11, suggesting that the chain is probably folded back under the mol., as obsd. in the crystal structure. Binding of McAbs to Cs was also affected by conformational modifications of the peptide ring that occur in some Cs-analogs. The results illustrate the potential of McAbs for probing the conformation of Cs-derivs. for which no structural data are available.

IT **114865-26-8**
RL: PRP (Properties)
(conformation of, monoclonal antibodies recognition of)

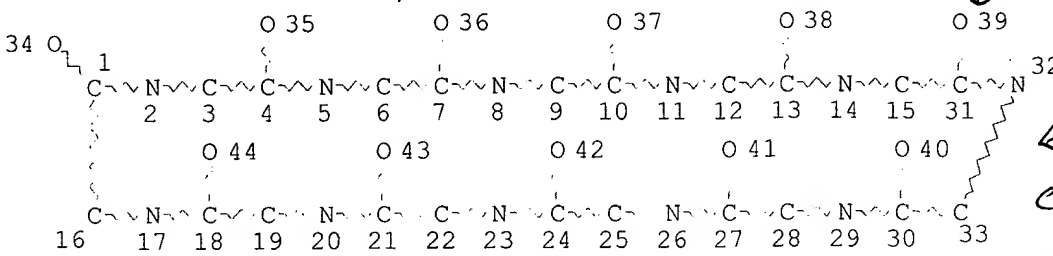
RN 114865-26-8 HCAPLUS
CN Cyclosporin A, 6-[(3R,4R)-3-hydroxy-N2,4-dimethyl-8-oxo-L-2,8-diaminooctanoic acid]- (9CI) (CA INDEX NAME)



(4) MARPAT SEARCH

LIU 09/975,923

=> d que l21
L14 STR parent structure



all oxygens have a connectivity = 1, to make them c=o

← this is the cyclosporin ring skeleton

NODE ATTRIBUTES:
CONNECT IS E1 RC AT 34
CONNECT IS E1 RC AT 35
CONNECT IS E1 RC AT 36
CONNECT IS E1 RC AT 37
CONNECT IS E1 RC AT 38
CONNECT IS E1 RC AT 39
CONNECT IS E1 RC AT 40
CONNECT IS E1 RC AT 41
CONNECT IS E1 RC AT 42
CONNECT IS E1 RC AT 43
CONNECT IS E1 RC AT 44
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 44

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
MLEVEL IS ATOM ON RING NODES AND RING GROUPS
MLEVEL IS CLASS ON CHAIN NODES AND CHAIN GROUPS
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

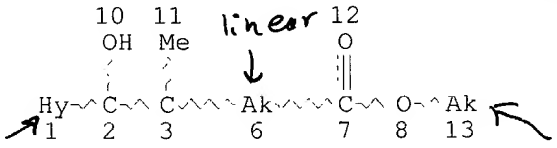
L16 50 SEA FILE=MARPAT SSS FUL L14 (MODIFIED ATTRIBUTES)

parent STR gives 50 citations

L19 STR

Subset STR that was searched against L16 parent set

cyclosporin ring



unsubstituted alkyl

NODE ATTRIBUTES:
CONNECT IS E2 RC AT 6
CONNECT IS E1 RC AT 13
DEFAULT MLEVEL IS ATOM
GGCAT IS LIN AT 6
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E22 C E11 N AT 1

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
MLEVEL IS ATOM ON RING NODES AND RING GROUPS
MLEVEL IS CLASS ON CHAIN NODES AND CHAIN GROUPS
ECLEVEL IS LIM ON ALL NODES

L21 2 SEA FILE=MARPAT SUB=L16 SSS FUL L19 (MODIFIED ATTRIBUTES) 2 citations - both are Applicant's stuff

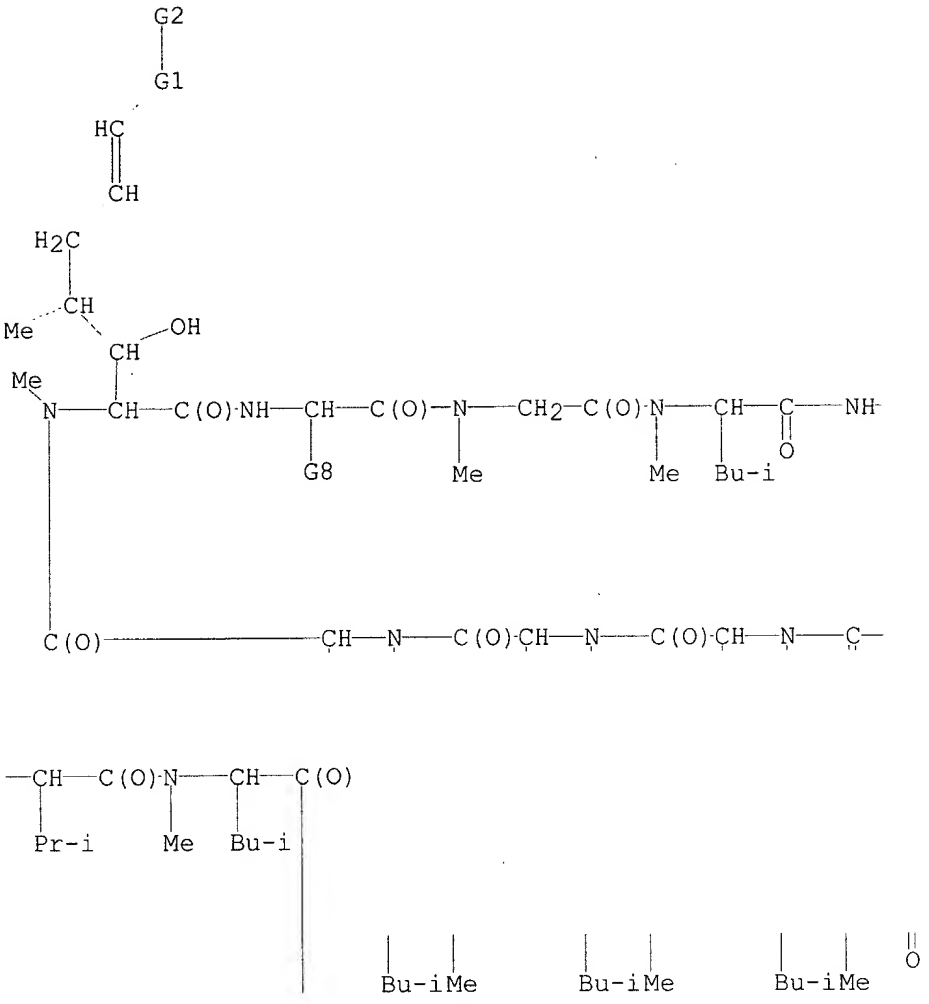
=> d ibib abs fqhit 1

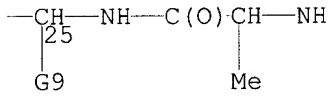
L21 ANSWER 1 OF 2 MARPAT COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:226601 MARPAT
TITLE: Cyclosporins for the treatment of respiratory diseases
INVENTOR(S): Or, Yat Sun; Lazarova, Tsvetelina; Hamann, Blake Christopher
PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002069902	A2	20020912	WO 2002-US6541	20020305
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002142946	A1	20021003	US 2001-800856	20010305
PRIORITY APPLN. INFO.:			US 2001-800856	20010305

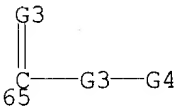
AB Novel semisynthetic cyclosporin analogs contg. different amino acids are synthesized for use as pharmaceuticals. The compds. can be used for th treatment of asthma, allergic rhinitis, bronchitis, etc. Thus, cyclosporin analogs were prepd. and their immunosuppressant activity was detd. by using the inhibition of the phosphate activity as the parameter.

MSTR 1





G2 = 65



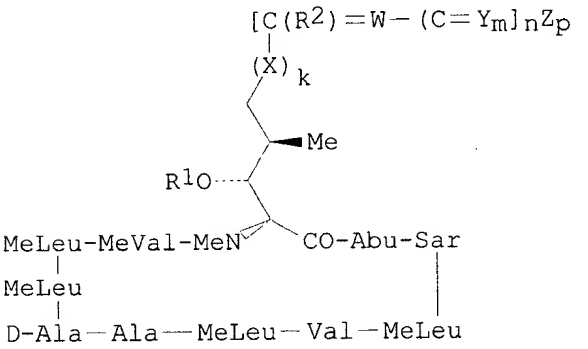
G3 = O
G4 = alkyl<(1-6)> (SO (1-) G5)
MPL: claim 1
NTE: or pharmaceutically acceptable salts
STE: 25-D

=> d ibib abs fqhit 2

L21 ANSWER 2 OF 2 MARPAT COPYRIGHT 2003 ACS
ACCESSION NUMBER: 111:127017 MARPAT
TITLE: Fluorescence polarization immunoassay for cyclosporin A and metabolites based on novel cyclosporin A derivatives
INVENTOR(S): Wang, Nai Yi; Wang, Philip P.; Morrison, Marjorie Anne
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 283801	A2	19880928	EP 1988-103397	19880304
EP 283801	A3	19900530		
R: BE, CH, DE, ES, FR, GB, IT, LI				
JP 63258491	A2	19881025	JP 1988-73057	19880325
US 5239057	A	19930824	US 1991-776890	19911015
US 5427960	A	19950627	US 1994-318570	19941005
PRIORITY APPLN. INFO.:			US 1987-31494	19870327
			US 1989-376244	19890706
			US 1991-776890	19911015
			US 1993-60598	19930512

GI

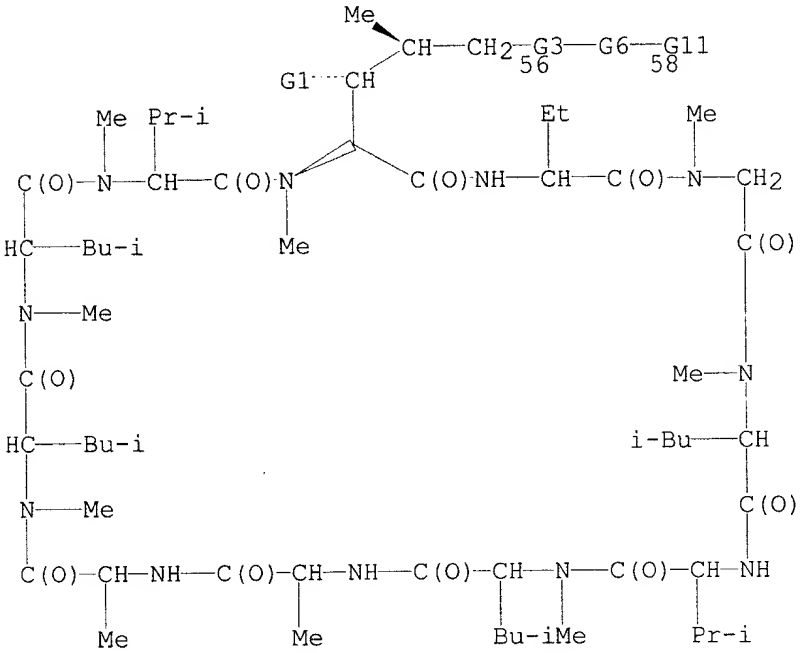


I

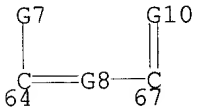
AB A method is described for prepn. of cyclosporin A derivs. I [k = 0-1 (k = 0 only if n = 1); m = 0-2; n, p = 0-1; R1 = H or a protecting group; R2 = H, lower alkyl, or CH(OH)Me; W = 1-20 (not including H) atoms of C, N, O, S, with .ltoreq.2 heteroatoms bonded together and with O never bonded to O or S; X = CH2, CHOH, C(O) (n = 0), or CH2OH (p = 0); Y = O, S, or NH; Z = a poly(amino acid), a poly(amino acid) deriv., a fluorescent moiety, OH, NH2, NHNH2, ORa, SRa, NHRa, NRaRb (Ra, Rb = stable C1-10 chain), SH, or a leaving group; MeVal, MeLeu, Sar, and Abu represent residues of N-methylvaline, N-methylleucine, sarcosine, and L-.alpha.-aminobutyric acid, resp.]. The derivs. are used as (1) immunogens in formation of antibodies specific to cyclosporin A and some metabolites, and (2) precursors in synthesis of fluorescent tracers having .gtoreq.1 epitope in common with cyclosporin A and some metabolites. Antibodies and tracers

are employed in a fluorescence polarization immunoassay (FPIA) for cyclosporin A and metabolites in biol. fluids. [6-(Carboxymethyloximino)-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylaminohexanoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R1, R2 = H; W = NOCH2; Y = O; Z = OH) (prepn. given) was conjugated to bovine serum albumin with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl, and the resulting immunogen was used to immunize exptl. animals. A fluorescent cyclosporin A tracer was prepd. from [7-carboxy-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylamino-6-heptenoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R2 = H; W = CH; Y = O; Z = OH) and aminomethylfluorescein-HCl. To serum or plasma samples was added pptn. reagent (30 mM NH4OAc in 98.5% aq. Me2CHOH). Following mixing and centrifuging, samples were analyzed with an automated assay employing an Abbott TDx Analyzer and a Cyclosporin and Metabolites Reagent pack. FPIA sensitivity was 15 ng/mL for cyclosporin A and metabolites. In a comparison of 208 clin. samples against an available RIA, linear regression anal. gave a slope of 1.153, an intercept of 21.06, and a correlation coeff. of 0.813.

MSTR 1B



G1 = OH
G6 = 64-56 67-58



G8 = CH
G10 = O
G11 = 73

G12—Ak
73 74

G12 = O
GGA = 74 76 <(1-10)>
MPL: claim 3
NTE: substitution is restricted
STE: 2-D